

FINAL ACTION

1. This action is responsive to the Amendment filed September 27, 2010, the Amendment including color drawings and a Petition under 37 CFR 1.84 filed October 1, 2010, and the Application Data Sheet (ADS) filed November 17, 2010. Claims 37 and 39 have been amended and claims 41-42 have been added. Claims 19-36, 38 and 40 remain withdrawn (see below), and claims 37, 39 and 41-42 are under consideration herein. Applicant's amendments and arguments have been thoroughly reviewed, and are persuasive in part. Particularly:

- a. Applicant's amendments to claims 37 and 39 were sufficient to overcome the prior rejections of claims 37 and 39 under 35 USC 112, first and second paragraphs, as the claims now clearly require particular expression patterns and may be interpreted by one skilled in the art; however, it is noted that these amendments have also **necessitated new grounds of rejection** under 35 USC 103 and 35 USC 112, first paragraph (new matter);
- b. Applicant's amendments to the specification and to claim 39 have overcome the objections at pages 4-5 of the prior Office action; and
- c. The new ADS filed November 17, 2010 has overcome the objection to the oath/declaration at page 5 of the prior Office action.

Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Color drawing petition disapproved

3. It is noted that the Petition for acceptance of color drawings under 37 CFR 1.84 filed October 1, 2010 has been disapproved as indicated on the enclosed PTO-90C. Accordingly, the color drawings of October 1, 2010 have not entered, and the objection to the prior version of the drawings (see paragraph 6 of the Office action of March 26, 2010) is maintained. Please see the enclosed PTO-90C for further information and guidance.

Election/Restrictions

4. Claims 19-36, 38 and 40 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention (claims 19-36) and non-elected species (claims 38 and 40), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 30, 2009.

5. This application contains claims 19-36, 38 and 40 drawn to an invention nonelected with traverse in the reply filed on November 30, 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Interpretation of amended claims 37 and 39

6. With regard to the amendment of claims 37 and 39 to reference “two or more marker genes identified in Table 2” and “wherein said two or more marker genes comprise SIAH-2 and DEME-6,” it is noted that the claims are now considered clear and definite to the extent drawn to the elected invention under consideration herein (which is

limited to the combination of the known genes SIAH-2 and DEME-6). However, as a courtesy to application, it is noted that should the claims be amended in such a way that rejoinder is required with respect to other genes listed in Table 2, the definiteness of the claims (as well as other issues under 35 USC 112, 1st paragraph) will be reconsidered in view of the fact that Table 2 appears to recite "genes" that are not clearly defined in the art.

7. Additionally, it is noted that despite the non-entry of applicant's color drawings for the reasons noted above, the meaning of "Cluster 1" and "Cluster 2" expression patterns may now be interpreted as stated in claims 37 and 39 as amended. Particularly, the claims now clearly require specific expression patterns for SIAH-2 and DEME-6 as indicators of "Cluster 1" or "Cluster 2" expression, such that the claims are clear to the extent that they are drawn to the elected combination of SIAH-2 and DEME-6 that is presently under consideration.

Claim Rejections - 35 USC § 112, first paragraph

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY
APPLICANT'S AMENDMENTS:**

8. Claims 37, 39, and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Independent claims 37 and 39 have been amended to require that reduced expression of SIAH-2 and DEME-6 serve as an indicator of a Cluster 1 expression pattern (and thus of recurrent cancer [claim 37] and of a negative prediction for progression free survival [claim 39]), while elevated expression of SIAH-2 and DEME-6 serve as indicators of a Cluster 2 pattern and of objective response (claim 37) and progression free survival (claim 39). It is noted that the originally filed specification discloses down regulation of SIAH2 in the primary tumors of patients resistant to tamoxifen (see, e.g., Example 4 at page 19), such that the originally filed specification provides adequate support for applicant's claim amendments with respect to SIAH-2. However, the originally filed specification fails to disclose such an expression pattern for DEME-6, such that applicant's amendments to claims 37 and 39 regarding DEME-6 add new matter. It is reiterated that the color version of Figure 2 filed October 1, 2010 has been denied entry (see above and enclosed PTO-90C), such that that Figure cannot be relied upon in support of applicant's amendments at the present time.

Claim Rejections - 35 USC § 103

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY
APPLICANT'S AMENDMENTS:**

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 37, 39 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ayers et al (US 7,504,222 B2 [March 2009; filed Oct 2002], previously cited) in view of Nakamura et al (US 7,531,300 B2 [May 2009; filed Sept 2004], previously cited).

Ayers et al disclose that estrogen receptor positive (ER+) and estrogen receptor negative (ER-) breast cancers respond differently to therapies that target the ER, and disclose detecting markers of ER+ cells in applications including assessing whether a tumor is ER+ or ER-, assessing the efficacy of anti-estrogen therapies (such as tamoxifen) for inhibiting cancer in a patient, and monitoring cancer progression (see entire reference particularly col 9, line 19-col 92, line 34). Ayers et al disclose identifying a patient as having an ER+ tumor based on a significant difference in expression level of a marker of Table 2 (an “ER positive marker”), wherein expression is compared to a control (col 92, lines 12-34). Table 2 of Ayer et al includes Deme-6 (see col 53), and it is noted that Table 2 is taught by Ayers et al as corresponding to ER+

markers that are overexpressed in ER+ tumors as compared to ER- tumors (see col 12, lines 10-26). Thus, Ayers et al disclose detection of Deme-6 overexpression as an indicator of an ER+ tumor, i.e., of a tumor more likely to respond to anti-estrogen therapy than an ER- tumor. Ayers et al do not disclose detection of SIAH2. However, Nakamura et al disclose that both SIAH2 and C1orf34 (i.e., DEME-6) exhibit statistically significant differences in expression in ER+ tumors as compared to ER- tumors (see entire reference, particularly col 38, lines 1-21 and Table 2). In view of the teachings of Nakamura et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have practiced methods in which significant overexpression of combinations of markers including Deme-6 and Siah2 are detected in a patient's primary tumor as an indicator of ER+ status and thus of objective response to anti-estrogen therapy (as set forth in claim 37) and/or of progression free survival (as set forth in claim 39). It is noted that Nakamura et al do not make clear what type of expression difference was observed with Siah2 (i.e., upregulation or downregulation in ER+ tumors). However, in view of the teachings of Nakamura et al, there were only two possible finite solutions from which to choose in order to allow the successful practice of the method suggested by Ayers et al in view of Nakamura et al (i.e., either Siah2 would be found to be upregulated or downregulated). An ordinary artisan could have readily pursued both of these known, finite alternatives with a reasonable expectation of success, such that the method of the claims would have been obvious to one of ordinary skill in the art in view of the teachings of Ayers et al and Nakamura et al (see MPEP 2143 E). With regard to the claim limitations related to "predicting outcome" (see

preambles and step (c) of claims 37 and 39), it is noted that this claim language requires no manipulative difference with respect to the methods suggested by Ayers et al and Nakamura et al, as the claims merely require drawing a mental conclusion regarding outcome based on a particular pattern of expression observed. The only manipulative steps actually required by the claims are those of analyzing a tumor with respect to expression levels of the elected genes SIAH-2 and DEME-6, and “determining if” those genes exhibit reduced or elevated expression as compared to any type of reference sample (such that the references clearly suggest the steps required by the claims). With further regard to dependent claims 41-42, Ayers et al further disclose the use of pools of normal and breast cancer cell lines (treated or untreated) as controls, such that the teachings of Ayers et al and Nakamura et al suggest the claimed invention (see entire reference, particularly col 98, lines 20-col 99, line 67).

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634